

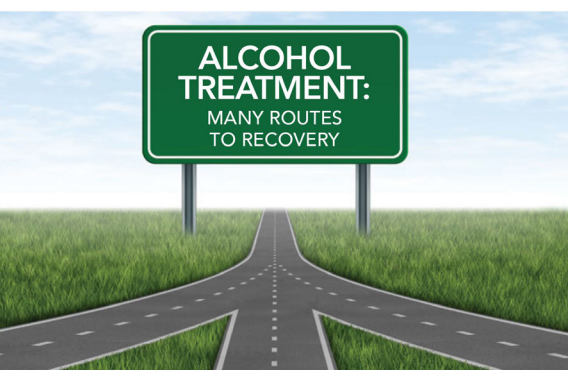
# NIAAA SPECTRUM

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

## FEATURE

### BRINGING ALCOHOL TREATMENT INTO THE MAINSTREAM



Nearly 15 million people in the United States have alcohol use disorder (AUD), but in any given year, less than 10 percent of them receive treatment. Even those who receive treatment may not receive the type of care that best fits their needs and improves their chances of a successful recovery. Research shows that about one-third of people treated for alcohol problems have attained abstinence a year later. Many others substantially reduce their drinking and report fewer alcohol-related problems. So, why do so many people who could benefit from treatment not receive it?

“Finding quality AUD care can often be complicated,” says NIAAA Director George F. Koob, Ph.D., “and many people aren’t aware of the full range of available treatment options. It can also be difficult to tell if a provider is offering evidence-based care that is grounded in clinical and health services research and has been demonstrated to produce positive treatment outcomes.”

NIAAA has been instrumental in the development and validation of much of today’s evidence-based treatments for AUD and continues to take the lead in the search for new and better treatments. An important aspect of NIAAA’s leadership in this area is communicating—to the public and caregivers—what quality AUD treatment looks like and where people can find it.

In 2017, NIAAA launched the Alcohol Treatment Navigator, a comprehensive online resource to help people search for professionally led, evidence-based AUD treatment. The Navigator educates consumers about AUD and treatment options, recommends 10 questions to ask a potential provider, and suggests 5 signs of higher quality treatment to recognize. It also provides help with searching for licensed professional therapists, specialty AUD treatment programs, and board-certified addiction doctors.

“The Navigator consolidates what health services research has learned over the past 20 years about the treatment system and indicators of good quality treatment,” says Lori Ducharme, Ph.D., NIAAA Program Director for treatment services research and lead developer of the Navigator. “I think its most important feature is that it brings together everything you need to know about alcohol treatment in one place and lays out actionable steps that the general public can understand and follow. The

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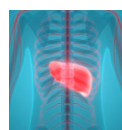


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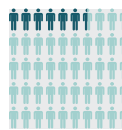


- 2 A New Treatment Strategy for Alcohol-Associated Liver Disease



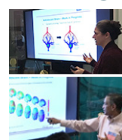
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## NEWS FROM THE FIELD

## REDUCTION IN DRINKING ASSOCIATED WITH IMPROVEMENTS IN HEALTH AND QUALITY OF LIFE



In clinical trials for alcohol use disorder (AUD), abstinence and no heavy drinking days are currently the only end points approved by the U.S. Food and Drug Administration. However, many individuals who do not achieve these end points may still reduce their drinking to less harmful levels during treatment.

A recent study published in *Alcoholism: Clinical and Experimental Research* suggests that reductions in drinking risk levels could be useful end points

for evaluating the effectiveness of AUD treatment for a given patient. Researchers conducted a secondary analysis of data collected from more than 1,000 individuals enrolled in NIAAA's Combined Pharmacotherapies and Behavioral Interventions study, also known as COMBINE. The COMBINE study, a clinical trial of medications and behavioral treatments for alcohol dependence (as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition), launched in 2001 and was conducted at 11 academic sites throughout the United States.

Researchers examined the COMBINE data for associations between reductions in drinking risk levels established by the World Health Organization (WHO) and improvements in physical health and quality of life.

WHO defines four levels of drinking risk, from low risk to medium, high, and very high risk (see chart below).

The researchers found that during treatment, reductions of one and two levels of WHO drinking risk (for example, reducing alcohol consumption from high risk to medium or low risk) were associated with significant reductions in blood pressure, improvements in liver enzyme levels, and significantly better quality of life measures. The researchers concluded that their findings suggest a reduction in WHO drinking risk levels could be a meaningful surrogate marker of improvement in how a person "feels and functions" after AUD treatment. They also note that "extending treatment options to target reductions in drinking, rather than complete abstinence, could expand the reach of alcohol treatment and have an important impact on public health."

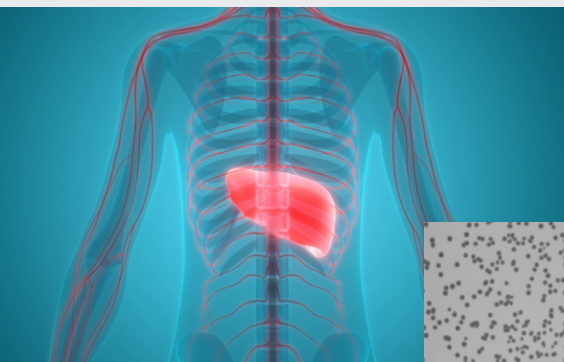
World Health Organization Alcohol Risk Levels (for males)				
	Low Risk	Medium Risk	High Risk	Very High Risk
Drinks per day (in grams)	1 to 40 g	41 to 60 g	61 to 100 g	101+ g
Drinks per day (in standard drinks)	0 to 2.9 drinks	3.0 to 4.3 drinks	4.4 to 7.1 drinks	7.2+ drinks
World Health Organization Alcohol Risk Levels (for females)				
	Low Risk	Medium Risk	High Risk	Very High Risk
Drinks per day (in grams)	1 to 20 g	21 to 40 g	41 to 60 g	61+ g
Drinks per day (in standard drinks)	0 to 1.4 drinks	1.5 to 2.8 drinks	2.9 to 4.3 drinks	4.4+ drinks

Source: Adapted with permission from Witkiewitz, K.; et al. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. *Alcoholism: Clinical and Experimental Research* 42(12):2453–2465, 2018.

## Reference:

Witkiewitz, K.; Kranzler, H.R.; Hallgren, K.A.; O'Malley, S.S.; Falk, D.E.; Litten, R.Z.; Hasin, D.S.; Mann, K.F.; and Anton, R.F. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. *Alcoholism: Clinical and Experimental Research* 42(12):2453–2465, 2018. PMID: 30395350

## NEWS FROM THE FIELD



Inset photo of *Lactobacillus reuteri*, courtesy of Jan Peter Van Pijkeren.

## A NEW TREATMENT STRATEGY FOR ALCOHOL-ASSOCIATED LIVER DISEASE

Alcohol is involved in nearly half of all liver disease deaths in the United States each year. Alcohol-associated liver disease (AALD) now replaces hepatitis C viral infection as the lead cause of liver transplantation due to chronic liver disease. Consequently, there is an urgent need for effective interventions for AALD, a complex

disease with multiple contributing factors. One of these factors is the change in the levels and types of bacteria in the gut (known as gut microbiota) that occurs as a result of chronic alcohol misuse. In a new NIAAA-funded study, a research team from the University of California, San Diego has identified an

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## FEATURE: *Bringing Alcohol Treatment . . . Continued from page 1*

addiction treatment system is confusing even if you know it inside out—we really tried to use the Navigator to help make sense of it all.”

Looking ahead, NIAAA will continue to help bring AUD treatment into the mainstream and make it a well-integrated component of the healthcare system. To that end, NIAAA is developing a complementary Clinician’s Navigator—a resource that leverages the Navigator to help physicians and other healthcare providers talk to their patients about treatment and assist with patient referrals. NIAAA is also developing a core clinician’s resource to give healthcare providers essential information they need to know about alcohol to recognize its effects across all domains of health and to help patients assess their risk and make better decisions.

### What Treatment Options Are Available?

A common misconception is that there are only two places to get help for alcohol problems—a 12-step program, such as Alcoholics Anonymous, or a long-term residential rehabilitation program. The reality is that evidence-based treatment comes in many forms.

AUD treatment settings include:

- Outpatient—visits to a physician’s or therapist’s office, or an outpatient treatment program
- Inpatient—overnight stays in a hospital for a specific period of time, with care provided by physicians and nurses who address psychological and physical health needs
- Residential—overnight stays at a treatment program for several weeks, with a full daily schedule of counseling, education, and wellness activities

The content of AUD treatment varies across these settings and depends on the patient’s specific needs and goals. Many patients benefit from counseling approaches, such as cognitive behavioral therapy or family therapy. Some patients benefit from medications

that help address craving and prevent relapse. Combining counseling and AUD medications can also be a very effective treatment approach.

### Expanding Medication Options

NIAAA supports a robust research program on the development of effective AUD pharmacotherapies. Currently, the U.S. Food and Drug Administration has approved three medications for treating AUD:

1. Naltrexone works by blocking the receptors in the brain involved in the rewarding effects of drinking and thus helps with craving. It comes as either a pill that is taken daily or an injection that can be given once per month.
2. Acamprostate is prescribed to help people with AUD maintain abstinence from alcohol by alleviating some negative symptoms of prolonged abstinence. It is a pill that is taken three times per day.
3. Disulfiram is a pill that causes unpleasant symptoms such as nausea and flushing of the skin when a person drinks alcohol. Wanting to avoid those unpleasant effects helps some people refrain from drinking.

“Not all people will respond to medications, but for some individuals, they can be an important part of overcoming AUD,” says Raye Litten, Ph.D., Acting Director of NIAAA’s Division of Treatment and Recovery Research and the Division of Medications Development. “NIAAA scientists are working to develop a larger menu of AUD pharmacotherapies. Future research will include studies to advance personalized medicine to match an individual to a specific medication for a more favorable outcome.”

To encourage the development of medications to treat AUD, NIAAA established a Human Laboratory Program to bridge the gap between preclinical studies and early Phase II clinical trials of candidate compounds. NIAAA also founded the Clinical Investigations Group, a network of clinical sites, to test the safety and

effectiveness of promising medications in early Phase II clinical trials. This program helps bridge the gap between preclinical studies and Phase III clinical trials involving larger groups of participants.

### Recovery and Relapse: What Does Successful Treatment Look Like?

Although definitions vary, one conceptualization of recovery from AUD is the disappearance of AUD symptoms accompanied by a state of well-being that builds resilience to relapse. Recovery is associated with neuropsychological and neurobiological changes; however, the process is not the same for everyone.

Some people with AUD need longer or more intense treatments, whereas others recover more quickly and with minimal intervention. Relapse is often a part of the process; it may take several attempts before someone can stop or reduce drinking over the longer term. A return

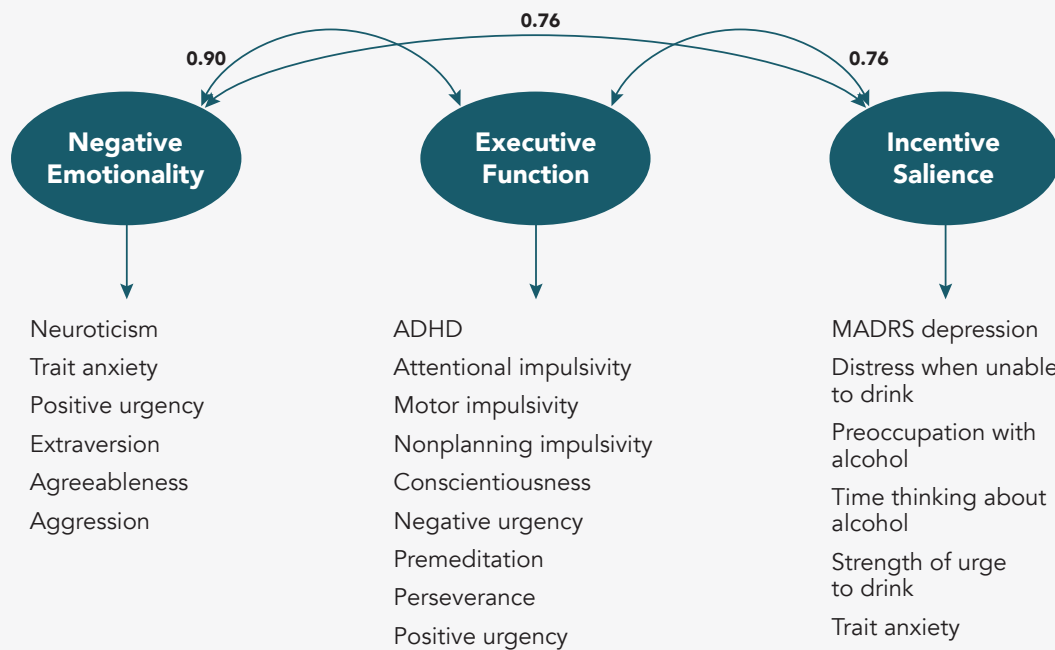
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## NEWS FROM THE FIELD

## IMPROVING TREATMENT BY MEASURING NEUROSCIENCE DOMAINS



Note: The arrows and coefficients represent cross-correlations between the factors, suggesting that treatment targeting one domain might affect the other domains as well. Factor correlation coefficients are 0.90, 0.76, and 0.76. ADHD = attention deficit hyperactivity disorder, MADRS = Montgomery-Åsberg Depression Rating Scale. Source: Adapted with permission from Kwako, L.E.; Schwandt, M.L.; Ramchandani, V.A.; Diazgranados, N.; Koob, G.F.; Volkow, N.D.; Blanco, C.; and Goldman, D. Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *American Journal of Psychiatry*. In press. PMID: 30606047.

Alcohol use disorder (AUD) is a common, heterogeneous disorder, and this heterogeneity drives the need for precision treatment. In a recent study, NIAAA investigators led by Laura E. Kwako, Ph.D., a Clinical Psychologist in NIAAA's Office of the Clinical Director, tested the hypothesis that neurofunctional domains could be established from neuropsychological studies of AUD subjects, which ultimately could lead to more effective individualized treatments. From a diverse clinical sample of individuals representing the spectrum of alcohol use and misuse, including patients seeking treatment for AUD, Dr. Kwako and her colleagues collected measures of addiction, personality, cognition, behavior, and exposure to early-life stress. Through factor analysis, they obtained factors corresponding to three functional processes considered relevant to addiction: (1) incentive salience:

giving increased motivational value to an object or event paired with alcohol, (2) negative emotionality: increased anxiety, negative mood, irritability, or other unpleasant feelings, and (3) executive functioning: how individuals organize behavior toward future goals and make choices. These three domains compose the main focus of the Addictions Neuroclinical Assessment (ANA), derived from social psychology and the neurobiology of addiction. Although the researchers note that more work is required to validate and standardize these domains for alcohol and other drugs, they are optimistic about the ANA's potential for providing a heuristic framework for improved diagnosis, prevention, and treatment. NIAAA researchers are currently collecting additional measures explicitly chosen to measure ANA domains.

"I think the ANA has the potential to fundamentally alter the way we think about alcohol and drug addiction and treatment," says Dr. Kwako. "Using these measures could really help us better understand the heterogeneity of AUD and more effectively tailor treatments to an individual."

NIAAA Director George F. Koob, Ph.D., a coauthor of the study, adds, "The ANA provides a heuristic framework for understanding the great advances that have been made and continue to be made in the neuroscience of addiction."

## Reference:

Kwako, L.E.; Schwandt, M.L.; Ramchandani, V.A.; Diazgranados, N.; Koob, G.F.; Volkow, N.D.; Blanco, C.; and Goldman, D. Neurofunctional domains derived from deep behavioral phenotyping in alcohol use disorder. *American Journal of Psychiatry*. In press. PMID: 30606047

## BY THE NUMBERS



Less than  
**10%** of people with  
past-year alcohol use  
disorder receive any  
treatment.

## TREATMENT OF ALCOHOL USE DISORDER IN THE UNITED STATES

Alcohol use disorder (AUD) is a common but undertreated health issue in the United States. According to a recent nationwide survey, the National Survey on Drug Use and Health (NSDUH), 14.1 million adults ages 18 and older, and 443,000 youth ages 12–17, had AUD in the past year. Of those individuals, it is estimated that only 6.5 percent of the adults and 5.2 percent of the youth received any

treatment. Under the direction of the Substance Abuse and Mental Health Services Administration, a component of the U.S. Department of Health and Human Services, NSDUH has been conducted in all 50 states and the District of Columbia every year since 1971 to assess Americans' substance use and mental health.

Population prevalence estimates (percentages) are weighted by person-level analysis and derived from the 2017 National Survey on Drug Use and Health public-use data file, defining "any treatment" as treatment or counseling designed to help reduce or stop alcohol use, including detoxification and any other treatment for medical problems associated with alcohol use, as well as defining AUD as alcohol abuse or alcohol dependence according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.

## NIAAA@WORK



## NIAAA DOCS TALK BRAIN AWARENESS WITH TEENS

On March 14, NIAAA scientists Mohammed Akbar, Ph.D., Rachel Anderson, Ph.D., Ivana Grakalic, Ph.D., and Soundar Regunathan, Ph.D., gave presentations on alcohol and the adolescent brain for teen students visiting the National Museum of Health and Medicine in Silver Spring, Maryland. The event was part of Brain Awareness Week, an annual program organized by the Dana Alliance for Brain Initiatives. Top: Dr. Grakalic discusses the function of neurons and synapses and the pruning process that takes place as the brain matures. Bottom: Dr. Regunathan shares brain imaging research and describes various changes that occur as the brain develops from childhood through adolescence.



## NOTEWORTHY

## NIAAA RECEIVES NATIONAL LEADERSHIP AWARD



On February 7, NIAAA, along with the National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA), received the National Leadership Award from the Community Anti-Drug Coalitions of America (CADCA) at the CADCA 29th National Leadership Forum. This annual award recognizes significant contributions to the field of substance abuse prevention. Pictured here, NIAAA Director George F. Koob, Ph.D., accepts the award on behalf of NIAAA from General Arthur T. Dean, Chairman and Chief Executive Officer of CADCA.

## NEWS FROM THE FIELD: A New Treatment . . . Continued from page 2

underlying mechanism for how alcohol-induced changes in gut microbiota may contribute to AALD. Building on this finding, the team demonstrated that engineered gut microbes could potentially provide a new treatment for AALD.

The research team, led by Bernd Schnabl, M.D., previously found that chronic alcohol consumption in animal models and in humans reduces the levels of an antimicrobial protein, known as regenerating family member 3 gamma (REG3G), in the intestines. The researchers' studies in mice have shown an increased level of REG3G protein in the intestine is protective against alcohol-induced liver injury. Making a connection between these findings and the knowledge that *Reg3g* gene expression is regulated by interleukin 22 (IL22)—a type of immune system molecule called a cytokine, which

regulates inflammation—Dr. Schnabl and colleagues investigated the effects of alcohol-induced gut microbiota changes on IL22 production and its role in AALD.

Using an animal model of AALD initially developed at NIAAA, the researchers found that alcohol reduces production of IL22 in the intestines by disrupting gut microbiota and lowering the levels of indole-3-acetic acid (IAA), a product of gut microbes. The researchers observed that administering IAA to mice in their food increased expression of IL22 and the *Reg3g* gene and reduced the severity of alcoholic steatohepatitis. Alcoholic steatohepatitis is a type of liver disease characterized by liver inflammation and fat accumulation in liver cells.

Next, the researchers sought to restore intestinal production of IL22 and engineered a common gut bacterial

strain to produce IL22. The bacteria were then fed to mice using the same animal model of AALD. Levels of IL22 and *Reg3g* gene expression in the gut were restored and associated with a reduced severity of alcoholic steatohepatitis, when compared with mice fed unengineered bacteria. These findings suggest gut bacteria could be manipulated to produce IL22 as a potential treatment for AALD.

## Reference:

Hendrikx, T.; Duan, Y.; Wang, Y.; Oh, J.H.; Alexander, L.M.; Huang, W.; Stärkel, P.; Ho, S.B.; Gao, B.; Fiehn, O.; Emond, P.; Sokol, H.; van Pijkeren, J.P.; and Schnabl, B. Bacteria engineered to produce IL-22 in intestine induce expression of *Reg3g* to reduce ethanol-induced liver disease in mice. *Gut*. In press. PMID: 30448775



## 5 QUESTIONS WITH . . .

### RAYE LITTEN, PH.D.

*Acting Director of the Division of Treatment and Recovery Research and Acting Director of the Division of Medications Development*



#### 1 You oversee NIAAA's treatment and recovery research and medications development—what are some research efforts you're pursuing?

Our work is geared toward finding new ways to treat alcohol use disorder [AUD] and to sustain recovery. Part of our portfolio supports clinical trials looking at medications that act on new targets in the brain to disrupt pathways of addiction. We hope these new medications will lead to more effective and safer treatments.

Recovery is another high-priority area. We are in the first stages of validating a universal definition of recovery that can be used across research studies. This will enable us to compare findings, identify which behavioral and pharmacological treatments work best and for whom, and invest resources into those treatments that will truly make a difference. We also are working to understand the different phases of recovery—such as short,

medium, and long term—and how they relate to the likelihood of relapse.

Finally, we are developing tools for health professionals to better engage patients across a wide array of practice settings, such as primary care, obstetrics-gynecology, gastroenterology, psychiatry, even pediatrics. We're striving to give professionals core skills for recognizing and treating alcohol-related problems and AUD.

#### 2 What are some challenges for your field?

So much of research relies on patients' self-reports about their experience with alcohol to measure treatment success. However, patients sometimes don't have a clear memory of their alcohol use. To overcome this assessment hurdle, NIAAA is working on an alcohol biosensor to measure alcohol content in the blood in real time. An effective biosensor would allow us to objectively assess alcohol intake without relying solely on patient recall—that would be a real game changer.

Another important area, across the National Institutes of Health, is personalized medicine. AUD is too complex for one treatment to work for everyone. Thus, various factors must be considered to successfully match an individual to a specific treatment. We need to determine a patient's characteristics—such as family history, AUD severity, and co-occurring disorders—together with objective biomarkers. We are interested in using such factors to develop an algorithm that would yield information on the best treatment for each person. This blending of science and novel computational analytical approaches is an up-and-coming area for NIAAA.

#### 3 What are some milestones in treatment research that have come about through NIAAA's efforts?

We were fortunate to have supported the development of naltrexone and acamprosate to treat AUD. Significant strides have been made in medications development in the past two decades, but a lot of work remains. NIAAA has built a network of sites to conduct early Phase II clinical trials, which are the most lengthy and costly part of drug development. Centralizing research at these sites has helped to complete trials faster while producing high-quality data. Within the past 10 years, the network has completed 5 clinical trials. A sixth trial will begin this summer.

Another NIAAA program focuses on using human laboratory models to screen for candidate compounds, bridging the gap between preclinical studies and early human testing. The Institute also encourages small business applications to facilitate the early-stage studies needed for an Investigational New Drug application to the U.S. Food and Drug Administration [FDA]. In addition, we have interacted closely with the FDA in its efforts to establish evidence-based guidelines for standardizing how AUD medications are assessed for regulatory approval.

Finally, we want to promote the use of evidence-based research information and tools by clinicians, patients, and their families. For broad audiences, NIAAA recently launched the Alcohol Treatment Navigator, an online resource that helps people understand what good, quality treatment looks like and to find alcohol treatment providers in their area. We are now working on a new core resource, similar to the

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**FEATURE: Bringing Alcohol Treatment . . . Continued from page 3**

to drinking after a period of abstinence is especially likely during times of stress and/or when individuals are exposed to people or places they associate with drinking. Currently, little is known about the factors that facilitate or inhibit long-term recovery, including why some people can recover without some form of treatment. A better understanding of the recovery process, including the factors that enable people to maintain changes in their drinking behavior and promote resilience to relapse, will inform the development of additional

effective treatment interventions and strategies to sustain recovery.

Because stress frequently triggers relapse, NIAAA is evaluating compounds that target brain stress systems and that could be used as potential medications for people susceptible to stress-related drinking. Researchers are also investigating whether patterns of brain activation can be used to identify people likely to relapse when exposed to certain stimuli, as well as whether particular AUD treatments are more effective in people with certain gene variants.

Finally, NIAAA also supports research on recovery support services and on technology that helps patients sustain the benefits of treatment.

“The challenges for improving AUD care may often seem insurmountable,” says Dr. Koob, “but recent advances and ongoing investigations reveal that opportunities for improving treatment options in all therapeutic domains for people with AUD are plentiful, and we will follow every opportunity to expand the effectiveness and delivery of AUD treatments.”

**5 QUESTIONS WITH: Raye Litten, Ph.D. . . . Continued from page 7**

Navigator, aimed at clinicians. We hope, through this initiative, to assist health professionals by making it even easier to access key information about AUD treatment. Another step will be to develop strategies to make evidence-based behavioral therapies and medications more accessible by integrating them into mainstream medicine. This includes increasing the use of evidence-based medications in clinical practice. Currently, less than 4 percent of AUD patients are prescribed FDA-approved medications. To make treatment more accessible, we need to leverage advances in technology and social media to engage patients and improve delivery of care.

#### 4 Looking ahead, what promising areas of investigation do you see?

Advances in several important research areas could significantly impact the discovery, development, and adoption of medications for AUD over the next decade. These include personalized medicine to improve treatment outcomes, the identification of new molecular targets for medications development, and efforts to increase the speed and efficiency with which promising compounds are tested. The latter will require innovations that bridge animal models with human laboratory testing and also develop

high-throughput screening to rapidly evaluate the potential usefulness of many different compounds.

#### 5 Outside of work, what favorite activities do you like to do?

I love being around my grandchildren and watching them participate in sports, plays, and dancing recitals. I belong to the Sandy Spring Lions Club, where I am involved in many community projects and have developed many new friendships. Finally, I enjoy watching sports, particularly football and baseball, and enjoy taking long walks with my wife.

**ABOUT US**

*NIAAA Spectrum* is NIAAA's triannual webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field.

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